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Gastrointestinal Lesions in Iron Deficient Premenopausal Women

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The cause of iron deficiency anemia (IDA) in premenopausal women is often presumed to be due to menstral losses. The purpose of this study was to investigate the diagnostic value of a comprehensive gynecologic and gastrointestinal evaluation among premenopausal women with IDA. Methods: 19 premenopausal non-pregnant women over 18 yrs of age with IDA defined by a HGB < 12 gm/dl with serum ferritin <10 ng/ml participated in the study. Evaluations included: directed history and physical examination by a specialist in gynecology and gastroenterology, EGD, colonoscopy, UGI small bowel follow through, antiendomysial antibody test and fecal occult blood tests. Results: Seven of 19 (37%) premenopausal women with IDA were diagnosed to have gynecologic cause of anemia by a specialist in that field. While only four of these seven patients had digestive complaints all but one (86%) were discovered to have gastrointestinal disease: DU, H pylori gastritis esophagitis and/or gastric AVM's. Of the 12 subjects without gynecologic source of anemia, GI evaluation each was identified to have significant GI disorders. Conclusions: Significant gastrointestinal disease is identifiable among most pre-menopausal women with IDA (18/19 or 95%), even when a careful evaluation by a specialist in gynecology suggests a gynecologic source. EGD should be considered in the evaluation of all premenopausal women with IDA and lower endoscopic examination should be reserved for those with suggestive symptoms or signs of colorectal disorders. Manuscript In Press, AM J Gastro.

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A Prospective, Multi-Discipline Evaluation of Premenopausal Women With Iron Deficiency Anemia

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ABSTRACT

The cause of iron deficiency anemia (IDA) in premenopausal women is often presumed to be due to menstrual losses. The purpose of this study was to determine the diagnostic value of a comprehensive gynecologic and gastrointestinal evaluation among premenopausal women with IDA. **Methods:** Nineteen premenopausal, non pregnant women over 18 yrs of age with IDA defined by a hemoglobin (HGB) < 12 gm/dl with serum ferritin (Fer) < 10 ng/ml participated in the study. Evaluations included: directed history and physical examination by a specialist in gynecology and gastroenterology, esophagogastroduodenoscopy (EGD), colonoscopy, upper gastrointestinal radiography with small bowel follow through (SBFT), antiendomysial antibody and fecal occult blood tests (FOBT). **RESULTS:** Seven of nineteen (37%) premenopausal women with IDA were diagnosed to have a gynecologic cause of anemia by a specialist in that field. While only four of these seven patients had digestive complaints all but one (86%) were discovered to have gastrointestinal disease by upper endoscopy: duodenal ulcer and H pylori gastritis (1), esophagitis and H pylori gastritis (1), erosive esophagitis (1), gastric arteriovenous malformations (AVM's, 1), nodular/erosive H pylori gastritis (2). Fecal occult blood testing was positive in only two (29%) subjects, upper endoscopy revealed erosive esophagitis and gastric (AVM's).

Twelve of the nineteen (63%) premenopausal women with IDA were not diagnosed to have a gynecologic source of anemia by a specialist in that field. Fecal occult blood testing was negative among all tested and the only digestive complaint was pyrosis in seven, each were identified to have esophagitis, duodenal ulcer or gastritis by upper endoscopy. Colonscopic examination of the twelve subjects without gynecologic etiology for IDA revealed: pan colitis (1), diverticulosis (1),

diverticulosis and melanosis coli (1), hyperplastic polyps (1) and nodular lymphoid aggregates (1).

Conclusions: Significant upper gastrointestinal disease is identifiable among most premenopausal women with IDA (18/19 or 95%), even when careful evaluation by a specialist in gynecology suggests a gynecologic source. Upper endoscopy should be considered in the evaluation of all premenopausal women with IDA and lower endoscopic examination may be reserved for those with suggestive symptoms or signs of colorectal disorders.

INTRODUCTION:

Iron deficiency among men and post menopausal women without a history of blood loss is recognized as an indication for gastrointestinal evaluation to determine a source of blood loss or malabsorption.[1-4] However, in premenopausal women where the most common gynecologic complaint is menorrhagia, menstrual losses are often presumed to be the source when IDA is identified.[5,6,7] The purpose of this study was to determine the diagnostic value of a comprehensive gynecologic and gastrointestinal evaluation among premenopausal women with IDA.

METHODS:

Inclusion Criteria:

Patients were referred from Primary Care, Internal Medicine, or Obstetric and Gynecology Clinics to the Gastroenterology Service for evaluation of iron deficiency anemia. The study was conducted at Fitzsimons Army Medical Center from March, 1995 to March, 1996 and then at Eisenhower Army Medical Center from January, 1997 to December, 1997. The protocol was approved by the Institutional Review Boards of both Medical Centers. Enrollment criteria included: premenopausal, nonpregnant women over 18 years of age giving informed written consent. All subjects underwent testing for hemoglobin content (Cell-Dyn 3,000, Abbott Labs, Abbott Park, Illinois) and serum ferritin (Abbott Enzyme Immunoassay, Abbott Labs, Abbott Park, Illinois). Iron deficiency anemia was defined by: hemoglobin (HGB) less than 12 gm/dL and serum ferritin (FER) less than 10 ng/ml .[8,9]

Study Evaluations:

All subjects underwent a directed history and physical examination by a subspecialist in gynecology and gastroenterology. Specific inquiry about gynecologic history included: age of

menarche, menstrual frequency, duration and quantity of flow (number of sanitary napkins or tampons used per cycle), symptoms of dysmenorrhea, and history of other gynecologic disorders. Menorrhagia was defined as duration of menstrual flow greater than seven days or greater than 80 ml of blood loss per day.[10,11] Each study subject underwent bimanual pelvic examination and pap smear by a gynecologist or nurse practitioner.

Directed history for evidence of gastrointestinal symptoms included: pyrosis, dysphagia, abdominal pain, diarrhea, evidence of bright or dark blood in the stool, change in bowel habits, and history of prior gastrointestinal disorders. All study subjects were asked about dietary intake, eating disorders, food fadism, pica and physical training. [12-21]

Each subject was asked to give urine and stool samples for occult blood testing (Bayer Multi-stick, Elkhart, Indiana and Hemoccult, Smith Kline Diagnostics, San Jose, respectively). All subjects underwent serologic testing for celiac disease with an antiendomysial antibody test (Scimedx Corporation, Danville, New Jersey).[22] Each subject underwent esophagogastrodudenoscopy with surveillance biopsy of the distal duodenum or proximal jejunum, colonoscopy, and upper gastrointestinal barium x-ray with dedicated small bowel follow through to evaluate for possible gastrointestinal source of iron deficiency anemia. [23,24,25]

RESULTS:

Demographics:

Twenty-six women meeting enrollment criteria were referred for study evaluation. Nineteen women gave written informed consent and participated in the study. Six patients were enrolled at Fitzsimons Army Medical Center, Aurora, Colorado and 13 were enrolled at Eisenhower Army Medical Center, Augusta, Georgia. Mean age of subjects was 40 yrs $\pm$ 2 (range 23-54 yrs).

Ethnicity was varied; ten African American, two Asian, five Caucasian and two Hispanic. The mean HGB and ferritin values were 10 ± 0.2 and 6 ± 0.6, respectively. Fifteen patients were dependent wives of active duty or retired soldiers and four were active duty soldiers. None of the subjects enrolled were strict vegetarians, had eating disorders or were long distance runners or tri-athletes. No subjects had recent surgery or obvious extra-intestinal or extra-gynecologic sources of blood loss. None of the subjects were within 36 months postpartum.

Gynecologic Evaluation, see Table 1,2 and Figures 1,2.

The mean age at onset of menarche for study subjects was 13 ± 0.4 yrs (range, 13-16 yrs). Gravida and Parity were $G_{2\pm0.4}$ $P_{2\pm0.3}$. Seven study subjects experienced symptoms of menorrhagia. Each was felt to have uterine fibroid(s) as the underlying cause of menorrhagia by a specialist in gynecology. Four of the seven have undergone hysterectomy and IDA has not recurred. Of the seven subjects with menorrhagia, six (86%) had upper endoscopic findings to include: duodenal ulcer and H pylori gastritis (1); erosive esophagitis and H pylori gastritis (1); erosive esophagitis (1); gastric AVM's (1); nodular H pylori gastritis (1); and erosive H pylori gastritis (1). Colonoscopic findings were remarkable only for the presence of hyperplastic polyps in two of these patients. Only one of the subjects with menorrhagia took periodic NSAID's and there were no upper or lower endoscopic findings in this patient. Directed GI history revealed four subjects to have active symptoms of pyrosis with three having esophagitis and or gastritis by upper endoscopy. The two subjects with persistently positive fecal occult blood tests, related no GI symptoms and were not on ASA or NSAID's, but each had endoscopic findings: erosive esophagitis and hyperplastic colon polyps (1) and gastric AVM's (1).

Of the twelve women without evident of a gynecologic source of IDA, all had upper

endoscopic findings: Barrett's esophagus and non-H pylori, erosive gastritis (1), duodenal ulcer and H pylori erosive gastritis (1), gastric AVM (1), gastric polyp and non- H pylori gastritis (1), nodular lymphoid gastritis (1), H pylori hemorrhagic gastritis, erosive duodenitis and H pylori gastritis (1), erosive esophagitis (1), and nonspecific, superficial gastritis (4). Colonoscopic findings were remarkable for the presence of pan colitis (1), diverticulosis (1), hyperplastic polyps (1), nodular lymphoid aggregates (1), and diverticulosis and melanosis coli (1). Each of the two subjects taking NSAID's were negative on fecal occult blood testing.

Gastroenterology Evaluation (see, table 2, figure 3)

Directed History

Of the eleven subjects that related a history of pyrosis, upper endoscopy revealed: erosive esophagitis and H pylori gastritis (1); erosive esophagitis (2), gastric AVM's (1), H pylori nodular gastritis (1), Barrett's esophagus and non-H pylori erosive gastritis (1), duodenal ulcer and H pylori erosive gastritis (1); non- H pylori gastritis and gastric polyp (1), H pylori hemorrhagic gastritis (1), H pylori gastritis and erosive duodenitis (1), and non-H pylori gastritis and erosive esophagitis (1).

One of the two subjects discovered to have a duodenal ulcer had a prior history of duodenal ulcer, but related no current digestive complaints. None of the subjects enrolled related a history of hematochezia, melena, abdominal pain, diarrhea or symptoms suggestive of malabsorption. Six subjects took aspirin or NSAID's periodically. Six patients were taking Histamine 2 blockers or proton pump inhibitors at the time of study evaluation, all had symptomatic pyrosis.

EGD Findings:

Upper endoscopy identified a duodenal ulcer in two patients. Both patients were Helicobacter

pylori positive, but neither patient had current symptoms of abdominal pain or was taking aspirin or non steroidal anti-inflammatory agents. Two subjects had one or more gastric AVM's. Endoscopic gastritis was identified in 15 subjects. Special stains of antral biopsies identified Helicobacter pylori among 7 of the 15 subjects with gastritis. Erosive esophagitis was seen in 4 subjects and one had histologically confirmed specialized columnar epithelium in a short segment of Barrett's esophagus, each had symptoms of pyrosis.

Colonoscopy Findings:

Colonoscopy was normal in all but 7 patients. Small hyperplastic colonic polyps were seen in three subjects, two had diverticulosis, one had nodular lymphoid aggregates, and one had aphthoid lesions throughout the colon and histologic confirmation of chronic colitis.

Small Bowel Follow Through and Other Tests:

Upper gastrointestinal series with dedicated small bowel radiography was normal in all subjects. Each of the small bowel biopsies revealed normal intestinal micro-architecture, and an absence of villous shortening or lymphocyte infiltration of the lamia propria. None of the subjects were positive on antiendomysial antibody test. Thirteen of the subjects had fecal occult blood testing. Two subjects were repeatedly positive for occult GI bleeding. Endoscopic and radiologic findings for these subjects included, one with asymptomatic esophagitis and hyperplastic rectal polyps and the other an asymptomatic gastric AVM's. The urinalysis was negative for blood in all subjects.

Dietary History:

Dietary history confirmed all study subjects to have an adequate caloric intake and none were strict vegetarians. Interestingly, seven of the nineteen subjects had a prior history of eating clay or

earth (geophagia) or dry granular laundry starch, Argo starch, Best Foods International, New Jersey, gloss starch (amylophagia) and each were from the South Eastern United States. Two of these seven subjects had positive fecal occult blood tests and all but one had findings on upper endoscopy: gastric AVM's (1), duodenal ulcer and H pylori gastritis (2), and esophagitis and gastritis (3). Four of the seven subjects with menorrhagia (57%) had a history of geophagia and/or amylophagia. Six of the nineteen study subjects related a prior history of eating ice (pagophagia), but only during the time of their pregnancies.

DISCUSSION:

The results of this pilot, investigation of premenopausal women with iron deficiency anemia identified a gynecologic cause of IDA in 7 of 19 (37%) subjects. However, even when the source of IDA was suspected to be gynecologic by a specialist in that field, significant upper gastrointestinal lesions to include duodenal ulcer (1), H pylori gastritis (4), esophagitis (3) and gastric AVM's (1) were discovered by EGD in 6 of 7 subjects (86 %). Importantly, a directed history by a gastroenterologist did not detect premonitory symptoms which would lead to routine upper endoscopic evaluation. Prior aspirin or NSAID's ingestion and the results of fecal occult blood testing were also unreliable in suggesting the presence of significant coexistent upper gastrointestinal pathology. Of the seven subjects with menorrhagia and gynecologic cause of IDA, none related lower gastrointestinal symptoms and Colonoscopy revealed only small hyperplastic colon polyps in 2 subjects.

Twelve of the nineteen (63%) premenopausal subjects with IDA did not have a gynecologic source of anemia. Directed history and physical examination revealed half of the subjects to have current digestive symptoms (all six had pyrosis) and one had a prior history of duodenal ulcer.

Fecal occult blood testing was negative in each of the subjects tested. All of the subjects with pyrosis were found to have esophagitis, ulcer, or gastritis by upper endoscopy. Of the six subjects without intestinal complaints, each had endoscopic findings: gastric AVM (1), non H pylori gastritis (1), nodular non H pylori gastritis (1), and non H pylori gastritis (2). None of these 12 subjects complained of lower gastrointestinal symptoms, yet one was found to have histologically confirmed chronic colitis, two subjects had mild diverticulosis, and one with small hyperplastic polyps and another with nodular lymphoid aggregates. Although endoscopic findings were evident among all of the subjects without a gynecologic cause of IDA, it is difficult to attribute the cause of IDA to the GI tract without identifiable macroscopic or microscopic bleeding. Perhaps the combination of "normal" menstrual blood loss, subclinical GI blood loss and/or nutritional factors are involved in the development of IDA among some premenopausal women. Also, the prevalent prescription of acid suppressant medications (6 of 19) may have healed more significant upper intestinal pathology and lead to underestimation of the severity of intestinal disease.

Unlike previous studies[2,3,4] evaluating the gastrointestinal findings among patients with IDA, our study cohort included only premenopausal women with IDA. This inclusion requirement lead to the evaluation of a younger and generally healthier cohort, with a mean age of 40 yrs. This is 20 to 23 yrs younger that the subjects studied by Rockey and Cello[2] and Kepczyk and Kadakia, respectively.[4] In our study no subjects were identified to have colon cancer or neoplastic polyps, while Rockey and Cello[2] and Kepczyk and Kadakia[4] each detected a 16% prevalence. Since age is a primary risk factor for colon cancer with over 90% of colon cancer detected in persons over 50 yrs of age,[26,27] it is likely that the absence of detection of neoplastic polyps and colon cancer in our

study is due to the younger age of our study cohort.

Zuckerman and Benitez have reported that 69% of their patients evaluated for occult gastrointestinal bleeding had no associated upper or lower digestive symptoms.[23] In fact, identification of either upper or lower endoscopic findings to explain occult bleeding or anemia was just as common among those subjects with as without referable complaints. Among our study subjects 11/19 (58%) had symptoms (pyrosis in all), but 18/19 (95%) had endoscopic findings. Like Zuckerman and Benitez,[23] we did not find that a directed GI history and physical examination or fecal occult blood testing helpful in excluding GI pathology. However when symptoms were present, GI findings were always detectable by endoscopy.

Eleven of nineteen subjects in this study had a history of PICA, six during pregnancy with pagophagia and six with either geophagia or amylophagia as a child or an adult unrelated to pregnancy. Although some investigators have suggested that amylophagia and geophagia may lead to iron malabsorption,[13,15,17] others have disputed this.[16] The frequency of PICA in our patients was 11/19 (58 %) and may reflect a sign or symptom of iron deficiency not a cause of IDA. Certainly, further careful investigation of this often unknown and regional phenomenon is warranted.

CONCLUSIONS:

Results of our study showed that IDA in premenopausal women is often (37%) due to menstrual blood loss. However the frequency of significant coexistent, chronic digestive disorders (6/7 or 86%) suggests that evaluation with upper endoscopy should be considered even when GI symptoms are absent.

Second, when the gynecologic source of IDA is not evident by careful evaluation, endoscopic

findings are common, 12/12 or 100%. Since directed GI history failed to suggest the presence of endoscopic findings in half of our patients, and symptoms of abdominal pain were absent in the two subjects with duodenal ulcers, it would seem reasonable to recommend upper endoscopy for all premenopausal women with IDA.

Our study subjects were young, mean age 40 yrs, and significant findings in the lower digestive tract were uncommon. The only subject found to have potential lower intestinal source of IDA had a normal menstrual history and subclinical pan colitis. Hence, it may be reasonable to reserve lower endoscopic examination to premenopausal women without a gynecologic etiology of anemia or those with directed lower digestive complaints.

Most of the women with IDA evaluated in our study (12/19 or 63%) did not have a gynecologic cause of anemia after directed history and examination by a specialist in that field. Although endoscopy identified significant digestive disorders (Barrett's esophagus, erosive gastritis and duodenitis, duodenal ulcer, pan colitis, etc) among many of the study subjects, it is difficult to attribute the cause of IDA to these findings without confirmation of active macroscopic or microscopic bleeding. To prove a causal relationship between these endoscopic findings and IDA will require effective treatment and long term resolution of IDA.

Legends

Table 1. Demographics: age, history of menorrhagia, history consistent with gynecologic source of iron deficiency.

Table 2. Demographics: GI history and endoscopic findings, results of FOBT and history of PICA. Abbreviations: GI, gastrointestinal; Hp+ (Helicobacter pylori positive); Hp- (Helicobacter pylori negative); ASA aspirin; NSAID, nonsteroidal anti-inflammatory drug; FOBT, fecal occult blood test; EGD, esopagogastroduodenoscopy, ND, not done; DU, duodenal ulcer, GERD, gastroesophageal reflux disease and (*) current use of histamine-2 antagonists or proton pump inhibitor medications.

Figure 1. Frequency of menstrual cycle, days

Figure 2. Duration of menstrual flow, days

Figure 3. Endoscopic findings among four of the study subjects: A) linear duodenal ulcer; B) gastric AVM; C) erosive gastritis; and D) hemorrhagic gastritis.

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Table 1.

Pt #	Age, years	Menorrhagia	Gynecologic Etiology
1	36	yes	Positive history, surgery
2	40	yes	Positive history, surgery
3	46	yes	Positive history, surgery
4	38	yes	Positive history, surgery
5	37	yes	Positive history, referred for surgery
6	28	yes	Positive history, referred for surgery
7	54	yes	Positive history, referred for surgery
8	46	no	Negative history
9	42	no	Negative history
10	35	no	Negative history
11	45	no	Negative history
12	44	no	Negative history
13	50	no	Negative history
14	45	no	Negative history
15	33	no	Negative history
16	44	no	Negative history
17	47	no	Negative history
18	23	no	Negative history
19	24	no	Negative history
	40 yrs $\pm$ 2	7 yes, 12 no	

Table 2

Pt #	GI History	ASA or NSAID	PICA	FOBT	EGD	Colonoscopy
1	none	no	yes	neg	DU, Hp+ gastritis	hyperplastic polyps
2	pyrosis, omeprazole	no	yes	neg	GERD, Hp+ gastritis	negative
3	pyrosis	no	ice	pos6/6	GERD	hyperplastic polyp
4	pyrosis	no	yes	pos2/2	gastric AVM's	negative
5	none	yes	yes	neg	normal	negative
6	pyrosis, nizatidine	no	no	ND	Hp+ nodular gastritis	negative
7	none, hx of ulcer	no	ice	neg	Hp+ erosive gastritis	negative
8	pyrosis, ranitidine	no	no	neg	Barrett's, Hp- erosive gastritis	pan colitis
9	pyrosis, hx of ulcer, famotidine	yes	yes, + ice	neg	DU, Hp+ erosive gastritis	negative
10	none	yes	no	neg	gastric AVM	diverticulosis
11	pyrosis	no	yes, + ice	neg	Hp- gastritis, gastric polyp	negative
12	none	no	ice	neg	Hp- Gastritis	negative
13	none	yes	ice	neg	Nodular lymph-oid gastritis, Hp-	hyperplastic polyp
14	pyrosis, omperazole	no	no	neg	Hp+ hemorrhagic gastritis	nodular lymphoid aggregates
15	none	no	no	ND	Hp- gastritis	negative
16	pyrosis, ranitidine	no	no	ND	Hp+gastritis, ero-sive duodenitis	Negative
17	none	yes	no	ND	Hp- gastritis	Diverticulosis, melanosis coli
18	pyrosis	yes	yes	ND	Hp- gastritis	negative
19	pyrosis	no	no	ND	Hp- gastritis, ero-sive esophagitis	negative

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Figure 1. Frequency of menstrual cycle, days

A Prospective, Multi-Discipline Evaluation of Premenopausal Women With Iron Deficiency Anemia
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Figure 2. Duration of menstrual flow, days

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Figure 3. Endoscopic findings among four of the study subjects: A) linear duodenal ulcer; B) gastric AVM; C) erosive gastritis; and D) hemorrhagic gastritis.

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Re: Manuscript #98-325

Dear Dr. McNalley:

Thank you for submitting a revision of your manuscript to the American Journal of Gastroenterology.

A PROSPECTIVE, MULTI-DISCIPLINE EVALUATION OF PREMENOPAUSAL WOMEN WITH IRON DEFICIENCY ANEMIA

Your revised manuscript has been reviewed by the editorial office, and I am pleased to accept it for publication in a future issue of the Journal.

I appreciate your thoughtfulness in making these changes and resubmitting your manuscript.

Yours Sincerely,

Eamonn M. M. Quigley, M.D., F.A.C.G.
Editor-in-Chief
American Journal of Gastroenterology

EMQ/lh